FRACTURES AMONG OLDER KIDNEY TRANSPLANT RECIPIENTS: A STUDY OF THE INCIDENCE OF FRACTURES, RISK FACTORS FOR INCIDENT FRACTURES, AND SUBSEQUENT MORTALITY

by
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ABSTRACT

BACKGROUND: Adult kidney transplant (KT) recipients are at greater risk of fractures than the general population, however, the burden of fractures has not been well studied in older KT recipients. Age plays a strong role in the risk of fractures and sequelae among older populations, in general. Therefore, the goals of this study were to identify the incidence of fractures, risk factors for fractures, and rates of subsequent outcomes in older KT recipients. We also tested whether epidemiology of fractures differs for older-old (defined in this paper as 55-64 years old) and younger-old (defined in this paper as ≥65 years old) age subgroups.

METHODS: 38,382 older (≥ 55 years) adult KT recipients who had Medicare primary coverage were identified through the USRDS registry. We estimated the cumulative incidence of post-KT fractures by age, sex, race, BMI and history of diabetes, in younger-old (55-64 years) and older-old (≥65 years) KT recipients. We identified risk factors of post-KT fractures for older

recipients using a Fine and Gray competing risk approach, accounting for the competing events of mortality and DCGL, and tested whether age modified the associations of sex, race, BMI and year of KT with post-KT fractures. We then tested whether post-KT fracture was a risk factor for subsequent mortality and DCGL using adjusted Cox proportional hazards models, and tested whether age, sex, race, BMI and year of KT modified the associations of post-KT fractures with morality and DCGL.

RESULTS: The cumulative incidence of post-KT fractures increased with age. The risk factors of post-KT fractures included recipient (age, sex, race, BMI, history of diabetes, time on dialysis, and peak PRA), transplant (year of KT, number of HLA mismatches), and donor factors (living donor, standard deceased donor, expanded criteria donor, and donation after cardiac death). In the younger-old group, diabetes (HR=2.35, 95% CI: 2.06-2.69) and White race (White vs. African American: HR=2.28, 95% CI: 1.92-2.69) were the two strongest risk factors; in the older-old group, underweight (HR=2.06, 95% CI: 1.29-3.28) and White race (White vs. African American: HR=2.11, 95% CI: 1.74-2.56) were the two strongest risk factors. Age (younger-old vs. older-old) modified the association between diabetes and post-KT fracture (younger-old: HR=2.35, 95% CI: 2.06-2.69, older-old: HR=1.74, 95% CI: 1.53-1.97, *P* for interaction=0.001). Post-KT fractures were associated with a 2-fold increase in subsequent mortality (HR=2.09, 95% CI: 1.94-2.25) and a 1.9-fold increase in subsequent DCGL (HR=1.87, 95% CI: 1.75-2.00) in the

older KT recipients. White race and diabetes modified the associations of post-KT fractures with mortality (White: HR=2.20, 95% CI: 2.01-2.41, non-White: HR=1.85, 95% CI: 1.62-2.11, *P* for interaction=0.03; diabetes: HR=1.93, 95% CI: 1.75-2.13, non-diabetes: HR=2.35, 95% CI: 2.10-2.63, *P* for interaction=0.008) and DCGL (White: HR=2.01, 95% CI: 1.85-2.18, non-White: HR=1.60, 95% CI: 1.43-1.78, *P* for interaction=0.001; diabetes: HR=1.76, 95% CI: 1.62-1.92, non-diabetes: HR=2.04, 95% CI: 1.85-2.25, *P* for interaction=0.03).

CONCLUSION: Older-old KT recipients had a higher risk of developing post-KT fractures. Recipients, transplant, and donor factors were associated with post-KT fractures. Older KT recipients who had post-KT fractures were at increased risk of both subsequent death and graft loss.

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INTRODUCTION

Kidney transplantation (KT) is an optimal form of renal replacement therapy (RRT) for patients with end-stage renal disease (ESRD).[1] Compared to hemodialysis, KT is a better treatment for all ages of ESRD patients, in terms of higher survival rate, fewer complications, improved quality of life, and increased cost-effectiveness.[2-3] KT has become increasingly preferred as a treatment option for older adults (age ≥55 years old) with ESRD. This increase is reflected in both the absolute number and the percentage of older KT recipients in each year: from 24% (2,138/8,878) of total KT recipients in 1988 to 57% (10,897/19,062) of total KT recipients in 2016, displaying a 137% increase.[4] McAdams-DeMarco and colleagues found that KT in older ESRD patients decreased mortality and graft loss from 1990 to 2011.[5] Similarly, among KT recipients aged 60-74 years, survival was improved within the first year post-KT, with a projected increased life span of 5 years and a 61% decrease in long-term risk of death.[6] These findings demonstrate that older ESRD patients still benefit from KT, despite multiple comorbidities and complications, particularly in terms of life expectancy.[7]

Although KT has demonstrated benefits in terms of life expectancy, some negative age-related outcomes emerge from the longevity benefit of KT, such as fractures. Fragility fractures occurring in the hips, vertebrae, or forearm (especially: distal forearm, distal radius, or wrist) are generally at higher prevalence in older populations.[8] However, even among middle-aged KT recipients, the incidence rate of hospitalization for fractures is 4.59 times greater than the rate in the general population.[9] Additionally, hip fractures in middle-aged KT recipients were associated with a 2.01 times increase in one-year all-cause mortality, compared to those not experiencing hip fractures.[10] Risk of fracture and possible negative sequelae in older KT recipients may be increased compared to middle-aged recipients, although this is not well-studied in the literature.

As is observed in general population ≥55 years old, several key distinctions can be made between younger and older individuals, such as the differences in osteoporosis,[11] functional decline,[12] and mortality rates,[13] creating two age subgroups: the “younger-old” and the “older-old”. We assumed that the same distinctions would also exist in the older KT recipients, specifically, variations in the risk of fractures by age subgroups, which may be due to differences in bone density, injury-causing mechanism, and degenerative changes affecting biomechanics in bones.[14] Given that the incidence rates of vertebral fractures increased with age in community-dwelling older adults,[15]

we hypothesized that the risk of fractures would also increase with age among older KT recipients. The subsequent outcomes of fractures also vary between age subgroups in hospitalized individuals ≥65 years old who experienced hip fractures, demonstrated by worse walking ability at discharge and lower survival prognosis for the older-old group.[16-17] Therefore, we expect to observe similar differences between younger-old and older-old age subgroups in KT recipients similarly.

A risk factor investigation for all-type fractures has never been exclusively conducted for older KT recipients,[9-10, 18-20] although they are among the highest risk of developing post-KT fractures. The goals of this study were to 1) investigate the cumulative incidence of post-KT fractures, 2) explore potential risk factors of post-KT factures, and 3) examine the possible association between post-KT fractures and their sequelae, all conducted in older KT recipients. Additionally, we tested whether the epidemiology of fractures differs for older-old (55-64 years old) and younger-old (≥65 years old) age subgroups.

METHODS

DATA SOURCES AND STUDY POPULATION

We identified 38,382 older adult (≥55 years) first KT recipients who underwent kidney-only transplantation between 1/1/1999 and 12/31/2011, using data from the United States Renal Data System (USRDS) and the Scientific Registry of Transplant Recipients (SRTR). The USRDS is the US national registry of KT recipients and patients with ESRD,[21] linked with the Centers for Medicare & Medicaid Services (CMS) and the United Network for Organ Sharing (UNOS).[22] SRTR is a national registry that includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the member of the OPTN. The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provided oversight to the activities of the OPTN and SRTR contractors. We included only KT recipients for whom Medicare was their primary payer in the 60-day post-KT period, which is standard for the majority of KT recipients.[23]

RISK FACTORS OF FRACTURES

The potential risk factors included: recipient factors (age, sex, race, cause of ESRD, body mass index [BMI], body weight, history of hypertension, history of diabetes, number of years on dialysis, and peak panel reactive antibody [PRA]), transplant factors (year of KT, number of human leukocyte antigen [HLA] mismatches, preemptive KT, and cold ischemia time), and donor factors (age, sex, race, living donor, expanded criteria donor, donation after cardiac death and standard deceased donor). The categories of the BMI were based on the WHO international classification: [24] "Underweight", "Normal Range", "Overweight" and "Obese".

POST-KT INCIDENT FRACTURE

We identified the first Medicare claim of fractures after KT as the incident fracture. The Medicare claim of fracture was based on the International Classification of Diseases-9th Modification Diagnosis Codes (ICD-9): skull, 800.x-804.x; neck and trunk, 805.x-809.x; upper limb, 810.x-819.x; and lower limb, 820.x-829.x, excluding pathologic fractures (733.1).[25]

MORTALITY AND DEATH-CENSORED GRAFT LOSS

As is standard with SRTR and USRDS data, mortality and death-censored graft loss (DCGL) were augmented through linkage with the Social Security Death Master File, data from the CMS, and waitlist data.[26] As we have previously defined, DCGL was irreversible graft failure signified by return to long-term dialysis (ascertained from CMS), listing for KT (ascertained from SRTR), or re-transplantation (ascertained from SRTR).[26]

CENSORING EVENTS

KT recipients who were free of post-KT fractures, DCGL, or death by the end of Medicare coverage or by the end of study (12/31/2011), whichever came first, were administratively censored.

STATISTICAL ANALYSIS

CHARACTERISTICS OF STUDY POPULATION

We compared the characteristics between the recipients who developed post-KT fractures vs. recipients who were free of fractures, in the younger-old and older-old groups. The continuous characteristics (age, BMI, body weight, years on dialysis, peak PRA, and cold ischemia time) were compared using Student's t tests. The categorical characteristics (sex, race, cause of

ESRD, history of hypertension and diabetes, years of KT, number of HLA mismatches, pre-emptive KT, and donor types) were compared using chi-square tests.

RISK OF POST-KT FRACTURES

For the time to fracture analysis, the time origin was the date of KT, and the time scale was years since KT. We identified both death and DCGL as competing events against incident fractures in post-KT periods, so we used Fine and Gray's proportional subhazards model to plot the cumulative incidence function by age categories.[27] We also used the "generate cumulative incidence in presence of competing events" methods[28] to estimate the cumulative incidence at several post-KT time points (1 year, 5 years and 10 years post-KT) under the competing risk framework, separately for younger-old and older-old groups, stratified by sex, races, BMI and history of diabetes, respectively.

RISK FACTORS FOR POST-KT FRACTURES

We used Cox proportional hazard models to identify what recipient, transplant and donors factors, were associated with post-KT fractures for the older KT recipients. The optimal multivariate model was selected based on the stepwise-AIC method.[29] Then we used Fine and Gray's proportional

subhazards model[27] to get the sub-hazard ratios (sHR) and their 95% confidential intervals for each factor included in the optimal model in younger-old group and older-old group. We included interaction terms in the subhazards model between age (younger-old vs. older-old) and sex, race, BMI, history of diabetes, year of KT, to test whether age modifies the risk of post-KT fracture in these subgroups. [30]

MORTALITY AND DEATH-CENSORED GRAFT LOSS AFTER POST-KT FRACTURES

We estimated the hazard ratio (HR) of mortality and DCGL, separately, using Cox proportional hazard regression models, considering the post-KT incident fracture as a time-varying exposure. We included interaction terms in the Cox proportional hazard models between post-KT fractures and age (younger-old vs. older-old), sex, race, BMI, history of diabetes, respectively, to test whether these covariates modify the association of post-KT fractures with mortality and DCGL.[30]

All statistical analyses were completed in Stata 12.0 (Stata, College Station, TX) and R 3.2.4.

RESULTS

STUDY POPULATION

Of the 38,382 older KT recipients who underwent KT from 1/1/1999 to 12/31/2011, 58% (22,274) were younger-old, and 42% (16,108) were older-old. There were 1,014 (4.6%) recipients who had incident fractures after KT in the younger-old group, and 1,056 (6.6%) in the older-old group.

In the younger-old group, the overall 10-year cumulative incidence was 10.0%. The 10-year risk of post-KT fractures was 8.9% for males, 12.7% for females, 12.2% for Whites, 8.2% for non-Whites, 10.0% for non-underweight recipients, 11.9% for underweight recipients, 13.1% for diabetic recipients, and 7.9% for non-diabetic recipients (Table 2).

In the older-old group, the overall 10-year cumulative incidence was 12.3%. The 10-year risk of post-KT fractures was 10.2% for males, 17.0% for females, 14.3%for Whites, 9.6% for non-Whites, 13.8% for non-underweight

recipients, 17.5%for underweight recipients, 14.9% for diabetic recipients, and 11.3% for non-diabetic recipients.

In the younger-old group, the KT recipients who developed post-KT fractures were more likely to be older (59.8 vs. 59.3 years old; $P<0.001$), female (48.2% vs. 37.9%; $P<0.001$), White (57.4% vs. 44.2%; $P<0.001$), and lower BMI (27.7 vs. 28.3; $P<0.01$), less years on dialysis (3.2 vs. 3.5 years; $P<0.001$), with history of diabetes (63.9% vs. 47.9%; $P<0.001$) and the cause of ESRD being diabetes (54.4% vs. 38.5%; $P<0.001$) (Table 1). Additionally, recipients who had post-KT fractures were more likely to receive organs from White (73.2% vs. 67.8%; $P<0.001$), live donors (21.2% vs. 18.6%; $P<0.05$), and the KT took place in earlier years (50.4% vs. 30.4% in year 1999-2003; $P<0.001$).

In the older-old group, the KT recipients who developed post-KT fractures were more likely to be older (69.5 vs. 69.3 years old; $P<0.001$), female (47.9% vs. 35.7%; $P<0.001$), White (72.5% vs. 60.6%; $P<0.001$), and lower BMI (27.1 vs. 27.7; $P<0.001$), less years on dialysis (2.3 vs. 2.6 years; $P<0.001$), with history of diabetes (49.9% vs. 44.1%; $P<0.001$), without history of hypertension (86.4% vs. 88.7%; $P<0.05$) and the cause of ESRD being diabetes (41.3% vs. 33.9%; $P<0.001$). Additionally, recipients who had post-KT fractures were more likely to receive organs from younger (43.3 vs. 44.8 years old; $P<0.01$), White (77.5% vs. 73.3%; $P<0.01$), and standard deceased donors (48.5% vs. 44.5%; $P<0.05$), and were less likely to receive organs

from donation after cardiac death donors (4.2% vs. 7.3%; *P*<0.001), and the KT took place in earlier years (46.8% vs. 25.9% in year 1999-2003; *P*<0.001).

AGE AND POST-KT FRACTURES

The risk of post-KT fractures increased continuously with age at KT (Figure 1). The KT recipients aged ≥80 years had the highest risk of post-KT fracture among all the older KT recipients (HR=1.95, 95% CI: 1.22-3.12) compared to KT recipients aged 55-59 years, and the risk of post-KT fractures in the second oldest group (aged 75-79 years) was the second-highest (HR=1.93, 95% CI: 1.56-2.38) compared to group aged 55-59 years. The risk of post-KT fractures was 1.38-fold (95% CI: 1.23-1.57) higher for recipients aged 60-64 years; 1.52-fold (95% CI: 1.34-1.71) higher for recipients aged 65-69 years; 1.65-fold (95% CI: 1.43-1.91) higher for recipients aged 70-74 years, compared to recipients aged 55-59 years.

RISK FACTORS OF POST-KT FRACTURES

The final multivariate model included the following factors: recipient factors (age, sex, race, BMI, history of diabetes, number of years on dialysis, and peak PRA), transplant factors (year of KT, number of HLA mismatches), and donor factors (living donor, expanded criteria donor, donation after cardiac death and standard deceased donor) (Table 3).

In the younger-old group, for every 5-year increase in recipients' age, the risk of post-KT fractures increased 1.25-fold (95% CI: 1.12-1.40) independent of other recipient, donor and KT factors. Female KT recipients were at 1.58-fold increased risk of developing post-KT fractures compared to males (95% CI: 1.39-1.80). Compared to African American KT recipients, White (HR=2.28, 95% CI: 1.92-2.69), Hispanic/Latino (HR=1.61, 95% CI: 1.30-1.99), and Other/multi-racial (HR=1.62, 95% CI: 1.24-2.12) recipients had increased risk of having post-KT fractures. KT recipients who were normal (HR=1.38, 95% CI: 1.17-1.63) or overweight (HR=1.17, 95% CI: 1.01-1.37) were at increased risk of having post-KT fractures, compared to obesity BMI group. The underweight KT recipients were also at high risk (HR=1.65, 95% CI: 0.97-2.80) of developing post-KT fractures compared to obesity recipients, but the estimate was non-significant (P>0.05). KT recipients with history of diabetes were at 2.35-fold increased risk of having post-KT fractures (95% CI: 2.06-2.69). Compared to recipients transplanted during 1999-2003, recipients transplanted in 2004-2008 had a 0.81-fold (95% CI:0.70-0.93) decreased risk of post-KT fractures, and recipients transplanted in 2009-2011 had a 0.66-fold (95% CI: 0.55-0.80) decreased risk of post-KT fractures. The KT recipients with donation after cardiac death donor had a 1.41-fold increased risk (95% CI: 1.07-1.85) of post-KT fracture compared to those with living donors.

In the older-old group, for every 5-year increase in recipient's age, the risk of post-KT fractures increased 1.14-fold (95% CI: 1.04-1.23) independent of other recipient, donor and KT factors. Female KT recipients had a 1.70-fold increased risk of developing post-KT fractures compared to males (95% CI: 1.50-1.93). Compared to African American KT recipients, White (HR=2.11, 95% CI: 1.74-2.56), Hispanic/Latino (HR=1.44, 95% CI: 1.11-1.88), and Other/multi-racial (HR=1.61, 95% CI: 1.19-2.17) recipients were at increased risk of having post-KT fractures. KT recipients who were underweight (HR=2.06, 95% CI: 1.29-3.28) or normal (HR=1.29, 95% CI: 1.10-1.52) were at increased risk of having post-KT fractures, compared to obesity BMI group. KT recipients with history of diabetes were at 1.74-fold increased risk of having post-KT fractures (95% CI: 1.53-1.97). Compared to recipients transplanted during 1999-2003, recipients transplanted in 2004-2008 had a 0.79-fold (95% CI:0.69-0.90) decreased risk of post-KT fractures, and recipients transplanted in 2009-2011 had a 0.61-fold (95% CI: 0.50-0.73) decreased risk of post-KT fractures.

The risk of post-KT fractures associated with diabetes differed among younger-old and older-old recipients (*P* for interaction=0.001). The diabetic younger-old KT recipients were at 2.35-fold (95% CI: 2.06-2.69) increased risk of having post-KT fractures, whereas the diabetic older-old KT recipients were at 1.74-fold (95% CI: 1.53-1.97) increased risk of having

post-KT fractures. The impacts of sex, race, BMI and year of transplant did not differ (all *P>0.05*).

MORTALITY AND DEATH-CENSORED GRAFT LOSS AFTER POST-KT FRACTURES

Post-KT fractures increased the risk of both mortality and DCGL, in the younger-old group (mortality: HR=1.93, 95% CI: 1.72-2.15; DCGL: HR=1.73, 95% CI: 1.57-1.90), as well as in the older-old group (mortality: 2.12, 95% CI: 1.93-2.34; DCGL: HR=1.93, 95% CI: 1.76-2.10), independent of recipient, transplant and donor factors (Table 4).

The association between post-KT fractures and mortality/DCGL differed by White race (*P* for interaction, mortality: *P*=0.03; DCGL: *P*=0.001) in the older KT recipients. The White KT recipients who developed post-KT fractures were at 2.20-fold (95% CI: 2.01-2.41) increased risk of death, whereas the non-White KT recipients who developed post-KT fractures were at 1.85-fold (95% CI: 1.62-2.11) increased risk of death. The White KT recipients who developed post-KT fractures were at 2.01-fold (95% CI: 1.85-2.18) increased risk of DCGL, whereas the non-White KT recipients who developed post-KT fractures were at 1.60-fold (95% CI: 1.43-1.78) increased risk of DCGL. The association between post-KT fractures and mortality/DCGL differed by history of diabetes (*P* for interaction, mortality: *P*=0.008; DCGL: *P*=0.03) in

the older KT recipients. The diabetic KT recipients who developed post-KT fractures were at 1.93-fold (95% CI: 1.75-2.13) increased risk of death, whereas the non-diabetic KT recipients who developed post-KT fractures were at 2.35-fold (95% CI: 2.10-2.63) increased risk of death. The diabetic KT recipients who developed post-KT fractures were at 1.76-fold (95% CI: 1.62-1.92) increased risk of DCGL, whereas the non-diabetic KT recipients who developed post-KT fractures were at 2.04-fold (95% CI: 1.85-2.25) increased risk of DCGL. The impacts of age, sex and BMI on the association between post-KT fractures and mortality/DCGL were not statistically significant (all *P* for interaction>*0.05*) in the older KT recipients.

DISCUSSION

In this national study of post-KT fractures in 38,382 older recipients, the risk of developing post-KT fractures were lower in the younger-old group, compared to the older-old group. The 10-year cumulative incidences of post-KT fractures were higher in females, White, underweight and diabetic KT recipients, in both younger-old and older-old groups. The risk factors for post-KT fractures for older KT recipients included older age, female, White, underweight, history of diabetes, and early year of transplant. The association between diabetes and post-KT fractures was stronger in the younger-old recipients, compared to the older-old recipients. Older KT recipients who developed post-KT fractures were subsequently at 2-fold increased risk of death and 1.9-fold increased risk of DCGL. The associations of post-KT fractures with mortality and DCGL were stronger in the diabetic KT recipients, as well as in the White KT recipients.

Our findings of the 10-year cumulative incidences of post-KT fractures were 10.0-12.3%, which were in the range 8% to 26% of former studies.[9, 31-33] The

10-year cumulative incidences of post-KT fractures were higher in females than in males, which was similar in Ramsey-Goldman's study[31] of 600 patients receiving solid organ transplants from 1992 to 1996. Some of the risk factors of post-KT fractures in KT recipients overlapped with the risk factors of fractures in general population, such as older age, female, White, underweight and diabetes.[34-37] An additional risk factor in our study was earlier years of KT, which was also identified as a risk factor in Abbott's study[10] that followed up the U.S. KT recipients using the same database as our study from 1994 to 1997. This may be due to the shorter follow-up length in the KT recipients who had KT later. Diabetes had been identified as a risk factor for post-KT fractures in several studies,[9-10, 32, 38-40] and we expanded the study of this association and found that the associations between diabetes and post-KT fractures differed by age. The decreased association between diabetes and post-KT fractures in the older-old KT recipients may be due to the different compositions of diabetic types in the younger-old and older-old groups: type 1 diabetic patients were more likely to have lower bone mineral density (BMD) compared to non-diabetic people, whereas type 2 diabetic patients were more likely to have normal or higher BMD, even after controlling for body size;[41] the observed relative risk of hip fracture in type 2 diabetic patients were also lower compared to type 1 diabetic patients.[42]

The post-KT fractures increased the risk of mortality by 2-folds in the older KT recipients, which was a bit higher compared to 1.6-folds in the Abbott's study,[10] the differences may be due to the longer follow-up time (13 years vs. 3 years) and more types of fractures (all types vs. hip fracture) included in our study. We expanded the model to test for the risk of DCGL subsequent to the post-KT, and tested for the interaction terms between post-KT fractures and age, sex, race, BMI and history of diabetes. The decreased association of post-KT fractures with mortality and DCGL in the diabetic KT recipients may be due to that the diabetic patients were more likely to have fractures in foot and ankle, which would be less risky for death.[43]

The strengths of our study were that we used the most up-to-date data from USRDS, which is the largest national registry for KT recipients in the United States, with a reasonable longer follow-up, compared to other studies addressing the same study question using the USRDS dataset;[9-10, 19] we used the competing risk methods in analyzing the risk of post-KT fractures, which accounted for the high mortality and high graft loss rates after KT and provided appropriate estimates, compared to the Cox proportional hazard method. The limitations of our study were that we used ICD-9 code to identify the incident fractures post-KT, which may lead to an underestimate of incident fractures, as only one third of all vertebral fractures would present with signs and symptoms that would lead to a

medical encounter,[32] and we only included those who had records of medical treatment; verifying the post-KT fractures through medical records rather than radiological examinations would also lead to misclassification of the outcome; there would be unmeasured confounders of fractures which could not be captured in claims data, such as BMD.

CONCLUSION

Older-old KT recipients had higher risk of developing post-KT fractures. Female, White, underweight and diabetic recipients had higher risk of developing post-KT fractures, in both younger-old and older-old KT recipients. Recipients, transplant and donor factors can help identify which KT recipients would be more likely to develop post-KT fractures. The association between diabetes and the post-KT fractures was higher in younger-old KT recipients compared to older-old KT recipients. The post-KT fractures increased the risk of subsequent mortality and graft loss in the older KT recipients; this association was higher in White older KT recipients compared to non-White older KT recipients, and was higher in diabetic older KT recipients compared to non-diabetic older KT recipients. Evaluations of fracture risk should be made before KT so that preventive strategies for fractures could be performed post-KT in order to avoid the events of subsequent death and graft loss in older KT recipients.

Appendices:

Table 1. Kidney transplant (KT) recipients, stratified by age at KT and post-KT fracture.

	Younger-Old (55-64 years)			Older-old (≥65 years)		
	Fracture-free (n=21,260)	Fracture (n=1,014)	p-Value	Fracture-free (n=15,052)	Fracture (n=1,056)	p-Value
Recipient Factors						
Age [a]	59.3 (2.8)	59.8 (2.8)	<0.001	69.3 (3.7)	69.5 (3.8)	0.08
Female (%)	37.9	48.2	<0.001	35.7	47.9	<0.001
Race (%)			<0.001			<0.001
White	44.2	57.4		60.6	72.5	
African American	32.8	18.7		21.9	12.1	
Hispanic/Latino	15.4	16.2		10.9	9.2	
Other/multi-racial	7.5	7.7		6.5	6.2	
Cause (%)			<0.001			<0.001
Glomerular	13.4	8.8		12.9	12.2	
Diabetes	38.5	54.4		33.9	41.3	
Hypertension	21.9	13.4		25.7	18.6	
Others	26.3	23.4		27.6	27.9	
Body Mass Index [a]	28.3 (5.0)	27.7 (5.0)	<0.01	27.7 (4.7)	27.1 (4.8)	<0.001
Body Weight [a]	82.5 (17.6)	80.3 (17.8)	<0.001	80.3 (16.3)	77.9 (15.9)	<0.001
Hypertension (%)	87.4	87.9	0.67	88.7	86.4	<0.05
Diabetes (%)	47.9	63.9	<0.001	44.1	49.9	<0.001
Years on dialysis [b]	3.5 (3.2)	3.2 (3.1)	<0.001	2.6 (3.0)	2.3 (2.8)	<0.05
Peak panel reactive antibody [b]	2 (16)	2 (20)	0.11	0 (13)	0 (14)	0.19
Transplant Factors						
Years of transplantation			<0.001			<0.001
1999-2003	30.4	50.4		25.9	46.8	
2004-2007	32.9	34.0		34.1	37.5	
2008-2011	36.7	15.6		40.0	15.7	
Number of HLA mismatches (%)			<0.001			<0.001
0	8.6	11.7		9.4	14.9	
1-2	9.7	14.2		11.1	14.0	
3-4	40.9	40.7		40.1	39.7	
5-6	40.8	33.3		39.3	31.4	
Pre-emptive KT(%)	3.3	2.3	0.10	4.2	4.4	0.92
Cold ischemia time [b]	15.8 (11.1)	15.8 (11.0)	0.14	15.8 (12.0)	15.8 (11.0)	0.58
Donor Factors						
Age [a]	41.2 (15.5)	40.8 (14.8)	0.33	44.8(15.7)	43.3(16.0)	<0.01
Female (%)	45.4	44.9	0.76	47.4	48.8	0.42
Race (%)			<0.001			<0.01
White	67.8	73.2		73.3	77.5	
African American	14.7	10.0		12.0	8.3	
Hispanic/Latino	13.8	13.2		11.4	11.3	
Other/multi-racial	3.7	3.6		3.3	2.9	
Live donor (%)	18.6	21.2	<0.05	21.5	21.8	0.85
Expanded criteria donor (%)	18.7	16.8	0.14	26.7	25.6	0.45
Donation after cardiac death (%)	7.7	7.3	0.69	7.3	4.2	<0.001
Standard deceased donor (%)	55.0	54.7	0.89	44.5	48.5	<0.05

[a] Shown in mean (SD)

[b] Shown in median (IQR)

Table 2. Cumulative incidence (%) of post-KT fractures, by age at KT, sex, race, BMI, and history of diabetes.

Sex	Younger-old (55-64 years)			Older-old (≥ 65 years)		
	1 year	5 years	10 years	1 year	5 years	10 years
Male	1.3	4.8	8.9	1.8	5.9	10.2
Female	1.8	7.0	12.7	2.8	9.7	17.0
Non-White	1.1	4.5	8.2	1.5	5.6	9.6
White	1.9	6.9	12.2	2.5	8.3	14.3
Non-underweight	1.4	5.5	10.0	2.5	8.0	13.8
Underweight	2.9	7.5	11.9	6.8	16.0	17.5
Non-diabetic	1.0	3.5	7.9	2.1	7.2	12.5
Diabetic	2.0	7.9	13.1	2.5	9.1	14.9

Table 3. Risk factors of incident fracture after KT.

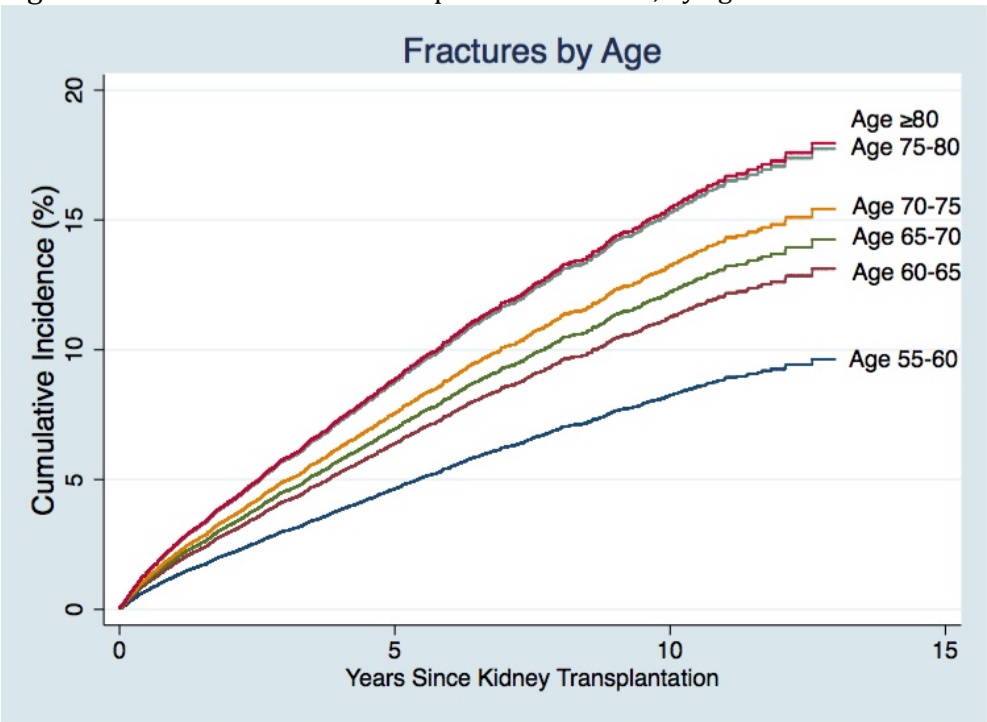
	Younger-old sHR (95% CI)	Older-old sHR (95% CI)
Recipient		
Age (per 5 years)	1.25 (1.12, 1.40)	1.14 (1.04, 1.23)
Sex		
Female	1.58 (1.39, 1.80)	1.70 (1.50, 1.93)
Male	Ref.	Ref.
Race		
White	2.28 (1.92, 2.69)	2.11 (1.74, 2.56)
African American	Ref.	Ref.
Hispanic/Latino	1.61 (1.30, 1.99)	1.44 (1.11, 1.88)
Other/multi-racial	1.62 (1.24, 2.12)	1.61 (1.19, 2.17)
Body Mass Index		
Underweight	1.65 (0.97, 2.80)	2.06 (1.29, 3.28)
Normal	1.38 (1.17, 1.63)	1.29 (1.10, 1.52)
Overweight	1.17 (1.01, 1.37)	1.10 (0.94, 1.29)
Obesity	Ref.	Ref.
Diabetes	2.35 (2.06, 2.69)	1.74 (1.53, 1.97)
Years on dialysis (per 3 years)	1.02 (0.95, 1.10)	1.04 (0.98, 1.10)
Peak panel reactive antibody (>50%)	1.14 (0.94, 1.37)	1.04 (0.86, 1.25)
Transplant		
Year of transplant		
1999-2003	Ref.	Ref.
2004-2008	0.81 (0.70, 0.93)	0.79 (0.69, 0.90)
2009-2011	0.66 (0.55, 0.80)	0.61 (0.50, 0.73)
Number of HLA mismatches		
0	Ref.	Ref.
1-2	1.13 (0.88, 1.45)	0.88 (0.69, 1.12)
3-4	0.95 (0.77, 1.16)	0.82 (0.68, 0.99)
5-6	0.94 (0.76, 1.17)	0.74 (0.61, 0.91)
Donor Type		
Living donor	Ref.	Ref.
Expanded criteria donor	0.98 (0.79, 1.22)	1.14 (0.94, 1.38)
Donation after cardiac death	1.41 (1.07, 1.85)	0.89 (0.64, 1.24)
Standard deceased donor	1.02 (0.86, 1.21)	1.10 (0.92, 1.30)

Table 4. Association of post-KT fractures with mortality and Death-Censored Graft Loss.

	Mortality	DCGL
Overall risk	2.09 (1.94, 2.25)	1.87 (1.75, 2.00)
Age		
55-64	1.93 (1.72, 2.15)	1.73 (1.57, 1.90)
≥65	2.12 (1.93, 2.34)	1.93 (1.76, 2.10)
P for interaction	0.199	0.104
Sex		
Female	2.12 (1.90, 2.37)	1.87 (1.70, 2.06)
Male	2.07 (1.87, 2.28)	1.87 (1.71, 2.04)
P for interaction	0.718	0.972
Race		
White	2.20 (2.01, 2.41)	2.01 (1.85, 2.18)
Non-White	1.85 (1.62, 2.11)	1.60 (1.43, 1.78)
P for interaction	0.029	0.001
Body Mass Index		
Underweight	1.74 (1.06, 2.88)	1.39 (0.88, 2.22)
Non-underweight	2.10 (1.95, 2.26)	1.87 (1.75, 2.00)
P for interaction	0.475	0.218
Diabetes		
No	2.35 (2.10, 2.63)	2.04 (1.85, 2.25)
Yes	1.93 (1.75, 2.13)	1.76 (1.62, 1.92)
P for interaction	0.008	0.025

All models are adjusted for the recipient, transplant, and donor factors listed in Table 3.
The *P* for interaction showed the statistical significance of effect modifications on the associations between post-KT fracture and mortality/DCGL.

Figure 1. Cumulative incidence of post-KT fractures, by age at KT.



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